2017년 제19차 대한산부인과내분비학회-학술대회 및 연수강좌

환경이상(미세먼지, 환경호르몬)이 생식 내분비에 미치는 영향

인제대학교 일산백병원

김영아

Epigenetics and Health Disparities

Alexis D. Vick[1,2] · Heather H. Burris[1,3,4]

Outcome	Black	White
Life expectancy (years) [50]	75.6	79.0
Cardiovascular disease (%) [67]	47.2	34.1
Hypertension prevalence (%) [67]	42.1	28.0
Breast cancer (age-adjusted rate per 100,000) [52]	122.9	124.4
Breast cancer mortality (age-adjusted rate per 100,000) [52]	28.2	20.3
Preterm birth rate (%) [5]	13.2	8.9
Low birth weight (%) [5]	13.2	7.0
Infant mortality rate (per 1000) [6]	11.1	5.1

African-Americans: exposed to higher levels of ambient air pollution

low socioeconomic status/ to live in dense urban centers

중국은 나쁜 공기 함께 마시며 평등 느껴

余华：中国在呼吸劣质空气中感受平等

[중국 소설가 위화, 서울국제문학포럼 참석차 訪韓]

중국 사회의 병폐와 모순 풍자... 미국·유럽서도 인정받은 작가

"한·중 관계, 사드에도 문제없어"

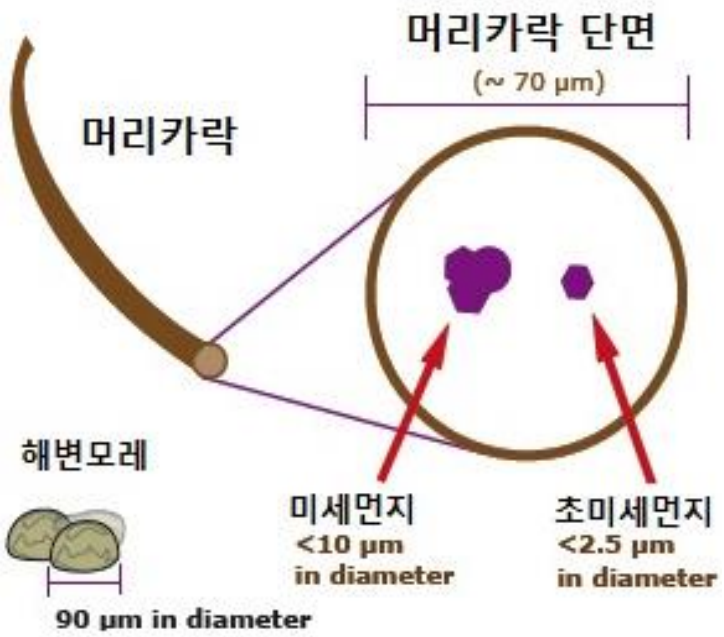
"중국 고위 관리들은 전 세계에서 가장 안전한 식품만 공급받아 먹는다. 인민의 식생활 안전엔 무관심해서 개선 노력을 하지 않는다. 10여 년 전부터 베이징은 스모그 문제가 심각하다. 인민들은 고위 관리들과 똑같이 나쁜 공기를 마신다는 점에서 평등을 느낀다."

미세 먼지(Fine dust, particulate matter(PM))

눈에 보이지 않은 아주 작은 물질/**1급 발암물질**
직경 10㎛ 이하의 입자상 물질

Table 1 Classification of particles according to their aerodynamic diameter

Particulate matter (PM)	Aerodynamic diameter (μm)
>PM_{10}	>10
Coarse particles (PM_{10})	≤10
Fine particles ($PM_{2.5}$)	≤2.5
Ultrafine particles ($PM_{0.1}$)	≤0.1
Nanoparticles	≤0.05



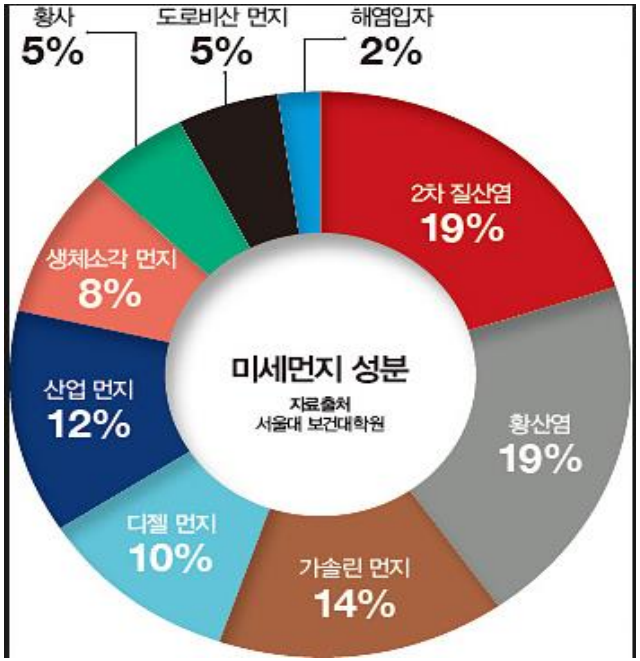
PM(particular matter)10(부유먼지)-지름 10μm이하인 먼지, 거대 분진, 대기 오염의 지표
-먼지, 꽃가루, 곰팡이
PM2.5:가장 몸에 해로운 미세먼지: 호흡기에서 걸러지지 않고 폐포까지 도달
-연소입자, 유기화합물, 금속

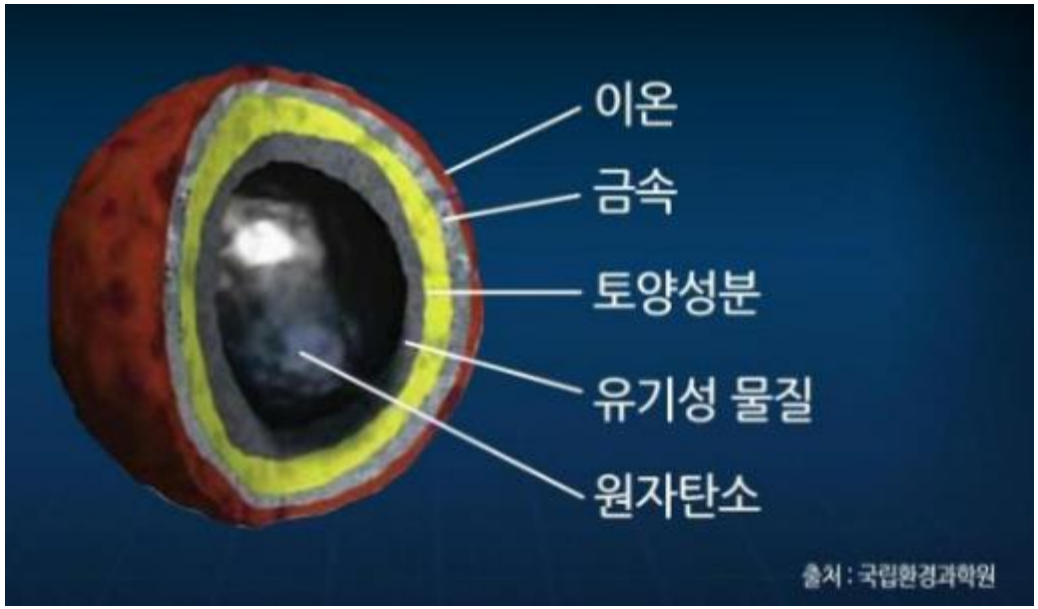
미세먼지와 황사의 차이점

황사가 중국 내륙 내몽골 사막에서 강한 바람에 의해 높은 대기로 올라간 흙먼지가 바람을 타고 이동해 지상으로 떨어지는 **자연현상**인 반면, 미세먼지는 자동차・공장・가정 등에서 사용하는 화석연료 사용으로 배출된 **인위적 오염물질**이 주요 원인이 된다. 미세먼지에는 중금속, 유해화학물질 등이 포함돼 있어 인체에 심각한 영향을 미치게 된다.

Different sources of air pollutants

-대기오염물질이 공기 중에 반응하여 형성된 덩어리(황산염, 질산염 등)와 석탄, 석유 등 화석 연료를 태우는 과정에서 발생하는 탄소류와 검댕, 지표면 흙먼지 등에서 생기는 광물로 구성

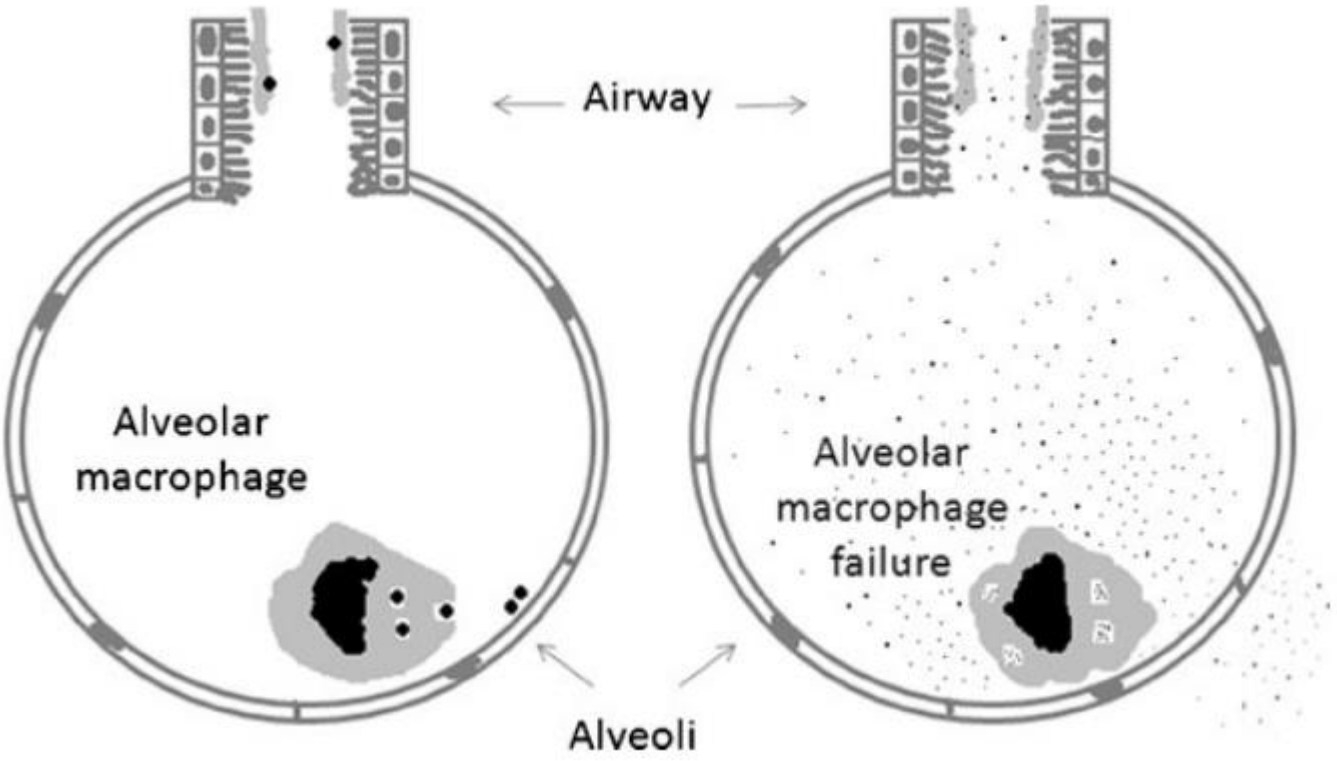




Air pollution and diseases: Epidemiologic and experimental studies

- Exacerbation of respiratory disease as asthma exacerbation of respiratory disease as asthma (Etzel 2003; Ko et al. 2007b)
- chronic obstructive pulmonary disease (COPD) (Ko et al. 2007a; Mayer and Newman 2001)
- respiratory infection (Lin et al. 2005; Medina-Ramón et al. 2006), lung cancer (Laden et al. 2007; Pope et al. 2002)
- increased number of emergency room visits (Farhat et al. 2005; Fusco et al. 2001)
- hospital admissions (Lee et al. 2006; Peel et al. 2005, 2007; Pope et al. 1995)
- School absenteeism and activity restriction.

✓ *코, 구강, 기관지에서 걸러지지 않고 우리 몸 속까지 스며든다*



Large surface area of particles in contact with alveolar surface

Macrophages failure in phagocyte **too many particle**

Release of mediators from the macrophages and epithelial cells due to activation of signaling pathways mediated by **oxidative stress, may then lead to inflammation** -**Larger extent on particle surface** area than on its composition

PM-induced oxidative stress

- Particles are able to induce the generation of free radicals-> increase in oxidative stress

Metals(Fe, Co, Cr, V)-redox cycling

Cd, Hg, Ni, Pb-deplete glutathione and protein-bound sulfhydryl groups (Stohs et al.2001; Stohs and Bagchi 1995; Valko et al. 2005)

- **Scavenger receptors (SR) :** human macrophages, neutrophils, and monocytes engaged in-phagocytosis.
- Different types of particles maybe ingested by the alveolar macrophage (AM) following **activation of diverse surface receptors.**

-> A dose dependent increase in dichlorofluorescin oxidation

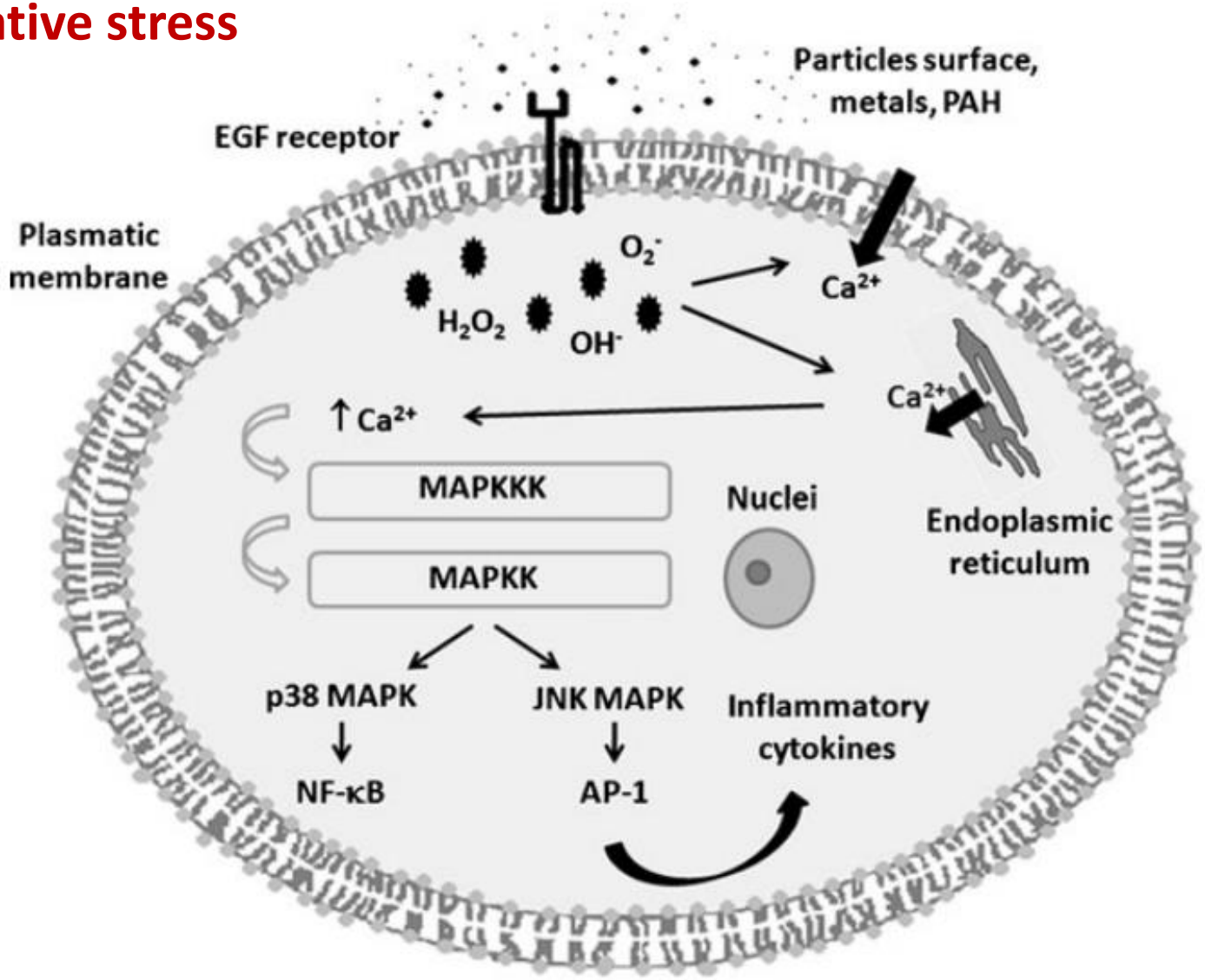
➢ **Which components of PM are responsible for phagocyte activation?**

Remains still unanswered- several components as **metal content, ultrafine particles (surface area), organic compounds and endotoxins** (Brown et al. 2001; Goldsmith et al.)

Organic fraction may probably contribute to pathological processes.

- **PAH** *(polycyclic aromatic hydrocarbons: 다환방향족탄화수소류는 내분비계 장애물질(환경호르몬)이자 발암 가능 물질이다)***induces the expression of cytochrome P450** in several lung cell types as AM, Clara cells and type 2 cells (Overbyet al. 1992). CYP1A1 can generate quinones, which **produce ROS by redox cycling** during their metabolic processing (Sorensen et al. 2003).
- PAH are absorbed and then distributed to tissues -> biotransformed by phase I metabolic enzymes to chemically reactive intermediates-> **covalently bind to DNA to form DNA adducts-**> mutation and originate tumor (Castaño- Vinyals et al. 2004; Sorensen et al. 2003).

PM-induced oxidative stress



Cell-derived ROS can result in increased intracellular calcium concentration, **activation and phosphorylation of the mitogenactivated protein kinase (MAPK) family**, thus initiating a cascade event, which may lead to an **increased gene transcription***(Adler et al. 1999; Pourazar et al. 2005, 2008; Thannickal and Fanburg 2000).*

Air pollution-epigenetics

- Higher exposure to air pollution has consistently been shown to be associated with **DNA methylation changes** *[Wang 2016, Zhong 2016, Breton 2016, Zhong 2015].*
- Wang et al. reported that per interquartile range increase (26.78 μg/m3) in 24-h exposure to fine particulate matter (PM2.5), **angiotensin-converting enzyme DNA methylation** (%5mC) was 1.12%lower
- Breton et al.(2016)

-Using newborn infant blood spots, Breton et al. found associations between **air pollution exposure** and **LINE-1 DNA methylation**. They also report that LINE-1 DNA methylation may affect **long term cardiovascular health risk.**

Preterm birth associated with maternal fine particulate matter exposure

- Maternal exposure to fine particulate matter**: a risk factor for preterm birth** (Shah et al., 2011), **low birth weight** (Holstius et al., 2012; Rich et al., 2015).
- PM2.5 exposure and preterm birth

:prospective cohort studies in Canada (Brauer et al., 2008) and China (Qian et al., 2016)

retrospective studies in the US (Ha et al., 2014; Huynh et al., 2006) and China (Fleischer et al., 2014), 'natural experiment' in the US (Parker et al., 2008).

- Proposed mechanisms

oxidative stress, pulmonary and placental inflammation, coagulopathy, endothelial dysfunction and hemodynamic responses (Kannan et al., 2006; Shah et al., 2011)

- Nachman et al. (2016) showed a **significant relationship between PM2.5 exposure and intrauterine inflammation .**

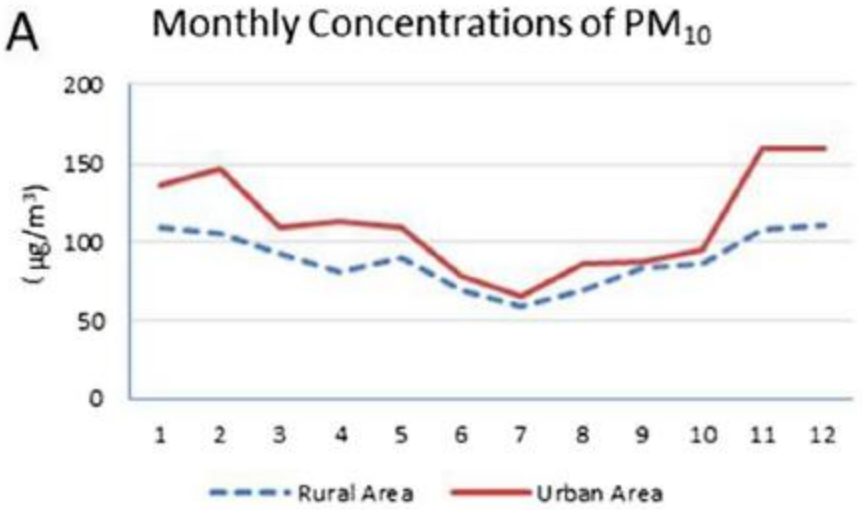
Contents lists available at ScienceDirect

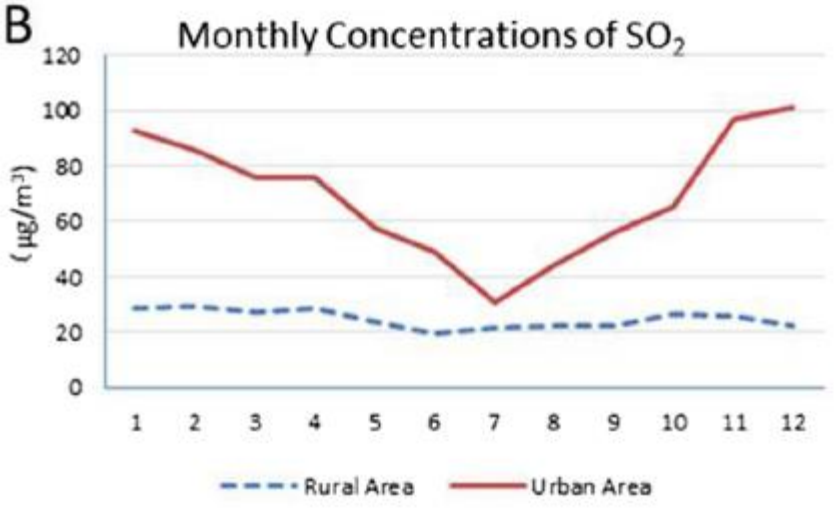
Environmental Pollution

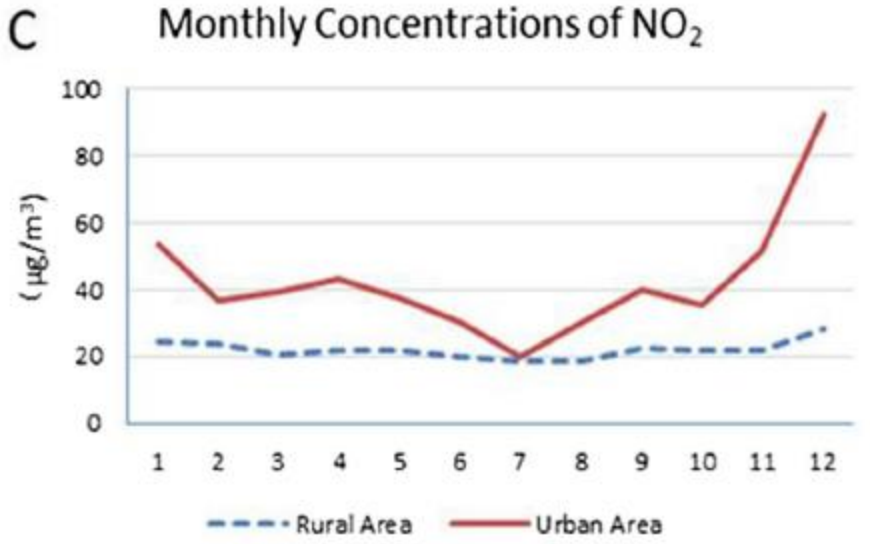
journal homepage: www.elsevier.com/locate/envpol

Air pollution and decreased semen quality: A comparative study of Chongqing urban and rural areas

To investigate the association and effects of **air pollution level on male semen quality** in urban and rural areas, this study examines the outdoor concentrations of particulate matter (PM10), sulfur dioxide (SO2), nitrous dioxide (NO2) and semen quality outcomes for 1346 volunteers in both urban and rural areas in Chongqing, China.







Monthly air pollution data. The panel shows the monthly average concentrations and trends of PM10 (A), SO2 (B), and NO2 (C) in the ambient air in both urban and rural areas in 2007.

Multivariate analysis for semen parameters in men and PM10, SO2 and NO2 air pollutant concentrations.

Variables	PM_{10} (μg/m^3)		SO_2 (μg/m^3)		NO_2 (μg/m^3)	
	β (95% CI)	*p*-value	β (95% CI)	*p*-value	β (95% CI)	*p*-value
Semen volume (ml)	−0.042 (−0.009–0.014)	0.122	0.012 (−0.001–0.102)	0.620	0.016 (−0.012–0.065)	0.780
Sperm concentration (10^6/ml)	0.075 (0.021–0.109)	0.031	0.028 (0.001–0.063)	0.416	0.074 (0.000–0.220)	0.215
Progressive motility (PR, %)	0.079 (0.000–0.211)	0.114	−0.039 (−0.075 to 0.039)	0.327	0.065 (0.001–0.102)	0.057
Total motility (PR + NP, %)	0.074 (0.012–0.169)	0.069	−0.031 (−0.060 to 0.029)	0.220	0.043 (0.003–0.106)	0.132
Normal morphology (%)	−0.212 (−0.801 to −0.003)	<0.001	−0.378 (−0.915 to −0.008)	<0.001	−0.381 (−0.920 to −0.009)	<0.001
Motile sperm VCL (μm/s)	−0.160 (−0.803 to 0.680)	<0.001	−0.121 (−0.902 to 0.681)	<0.001	−0.160 (−0.721 to −0.001)	<0.001
Motile sperm VSL (μm/s)	−0.209 (−0.818 to −0.016)	<0.001	−0.129 (−0.250 to 0.018)	<0.001	−0.210 (−0.827 to −0.004)	<0.001
Motile sperm LIN (%)	−0.069 (−0.188 to 0.022)	0.069	−0.047 (−0.108 to 0.095)	0.179	−0.068 (−0.178 to 0.001)	0.057

After adjusting for ***age, education, BMI, smoking, drinking, abstinence time and season***, the outdoor exposure concentrations for PM10, SO2, and NO2 were found to be significantly and negatively associated with a normal sperm morphology percentage

Ovarian Damages Produced by Aerosolized Fine Particulate Matter ($PM_{2.5}$) Pollution in Mice: Possible Protective Medications and Mechanisms

Hui-Fang Gai[1,2], Jian-Xiong An[3], Xiao-Yan Qian[3], Yong-Jie Wei[4], John P Williams[5], Guo-Lan Gao[1,2]

Methods: Eighty-four ICR mice were divided into six groups: **control group, PM2.5 group, PM2.5 + aspirin group, PM2.5 + Vitamin C group, PM2.5 + Vitamin E group, and PM2.5 + ozone group**.

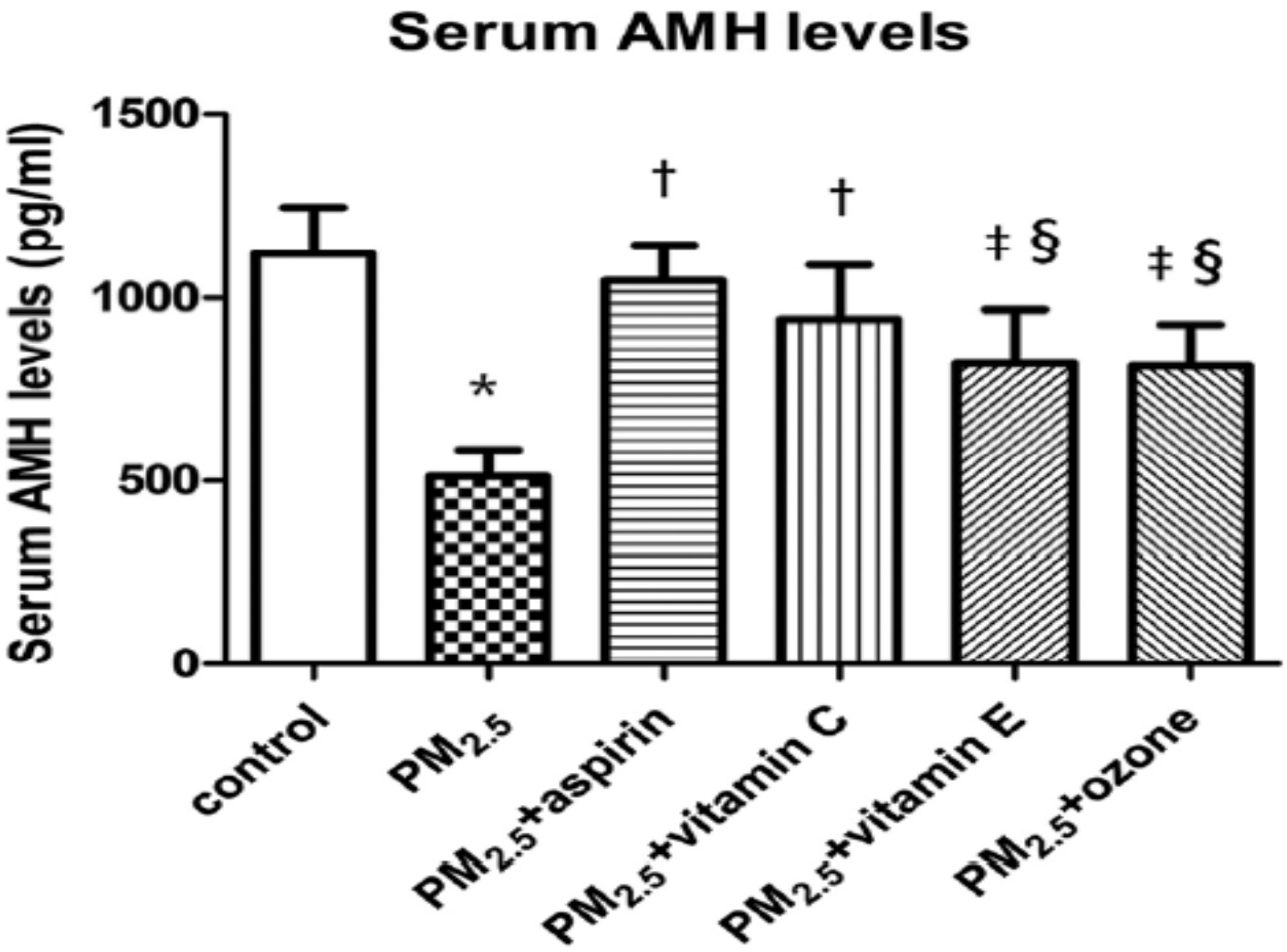
PM2.5 was given by intratracheal instillation every 2 days for 3 weeks.

Aspirin, Vitamin C, and Vitamin E were given once a day by oral gavage for 3 weeks

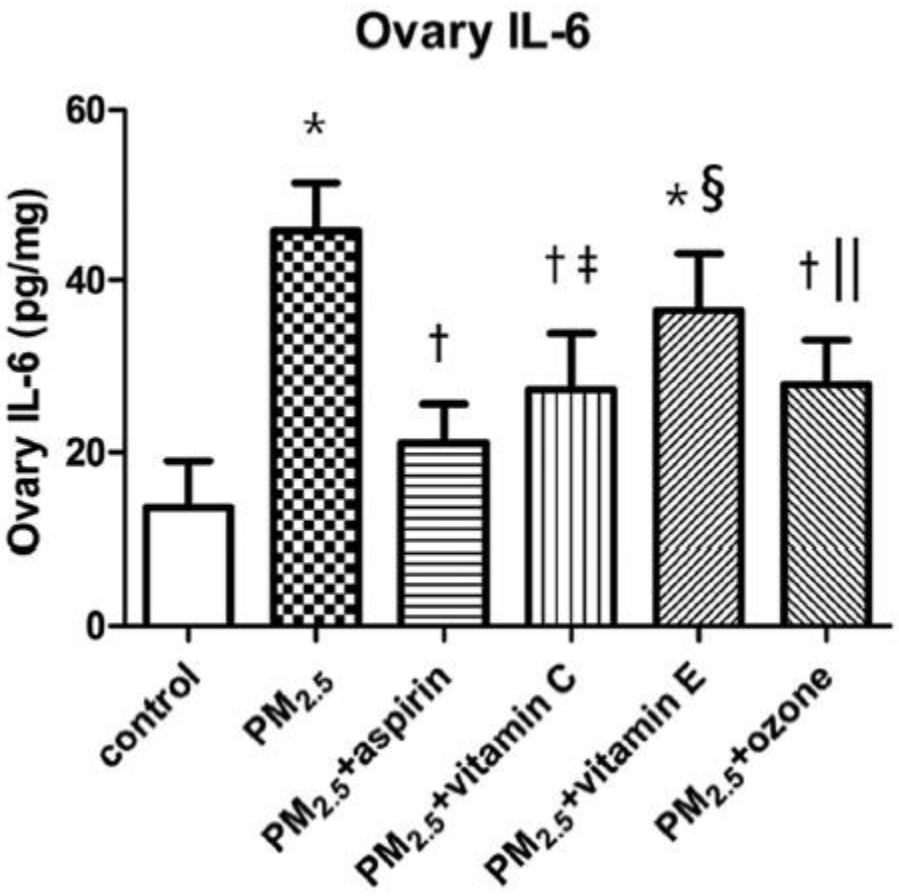
ozone was administered by intraperitoneal injection once a day for 3 weeks.

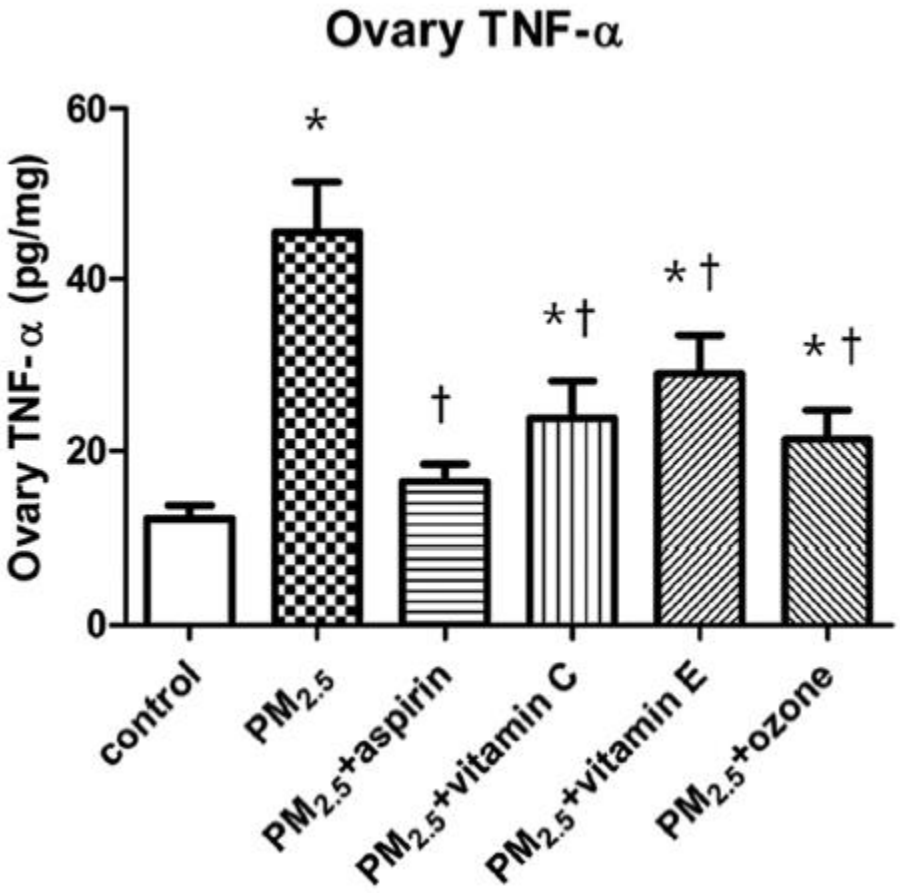
- **Aspirin**-anti-inflammatory effects and antioxidant effects
- **Vitamin C (ascorbic acid)-** antioxidant & prevent histamine release and increase the detoxification of histamine
- **Vitamin E**- effective antioxidant
- **Ozone**- potent oxidant but induce upregulation of antioxidant enzymes.

Effects of different medications and ozone on the levels of serum AMH in PM2.5-treated female mice.



Effects of different medications and ozone on the levels of ovarian inflammation in PM2.5-treated mice.





- ✓ Ovarian damage following exposure to PM2.5 was demonstrated by **hemorrhage, vascular congestion, and follicular degeneration.**

환경 호르몬

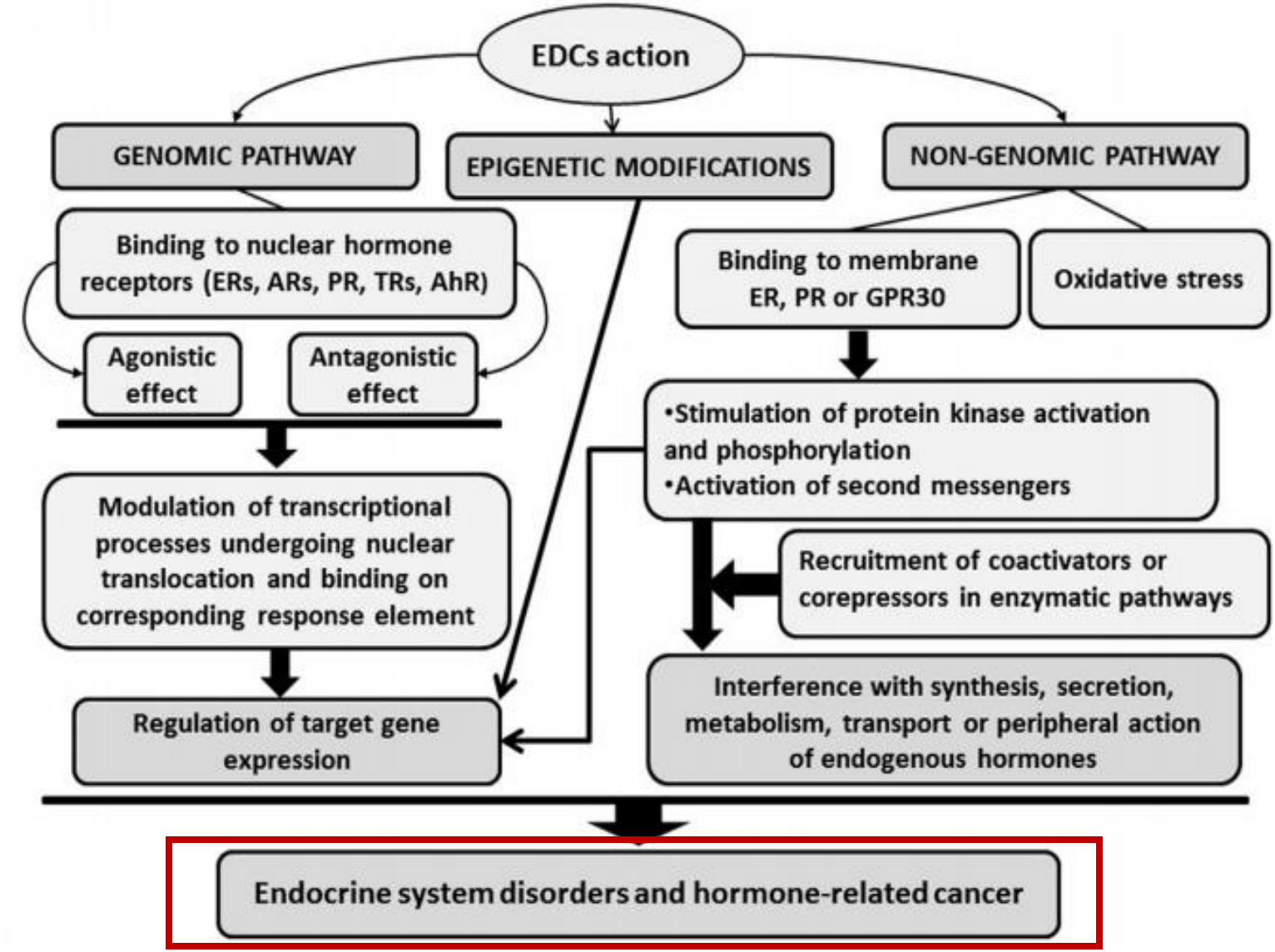
- 환경호르몬-일반적으로 생체 내에서 호르몬 유사기능을 하는 화학물질
- Endocrine Disrupting Chemicals (EDCs), 내분비 교란물질, 내분비 장애물질

  Endocrine Disruptor (ED)
- 내분비 체계의 기능을 바꾸는 외부물질(exogenous substance) 혹은 혼합물로 생명체 혹은 자손(progeny), 일부 사람들(subpopulation)에 부정적 건강의 영향을 미치는 것으로 정의하였다(WHO, 2002)
- Main targects: homeostasis of sex steroids and the thyroid
- Xenobiotics(생체 이물)-생체에서 생산되지 않는 인공화학 물질, 약물, 식품첨가물, 환경오염물질 등 생체에 대한 유해 물질의 총칭

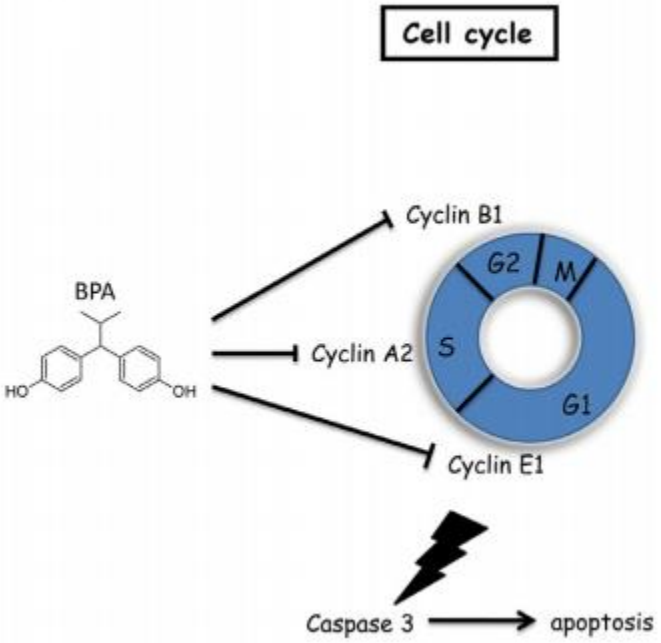
내분비 교란 물질들...persistent organic pollutant(POP)

제초제(dichloro-diphenyl-trichloroethane, DDT)
농약, 살충제, 항진균제류 (vinclozolin)
Dioxins and dioxin-like PCB(polychlorinated biphenyls) 산업용제나 윤활제로 사용되는 물질과 부산물들
플라스틱류(bisphenolA, BPA, single chemical):epoxy resins, can lining, thermal paper product, dental sealants, baby bottles, food containers, other plastic products
고분자화합물류(phthalate;DEHP,DBP,BBP,DINP,DIDP): PVC을 부드럽게 하기 위해 사용하는 화학성분, 화장품, 장난감, 세제, 목재 가공 및 향수 용매, 가정용 바닥재, 빨대
의약품으로 사용되는 합성 에스트로겐 (DES)
화장품성분과 세면도구(Parabens, UV-screen)
중금속(수은, 납, 카드뮴)

Potential mechanism(s) of endocrine disrupting chemicals (EDCs) action



Alternative mechanisms of action



MEHP : affect ovarian follicle health by inducing the **generation of ROS** and by

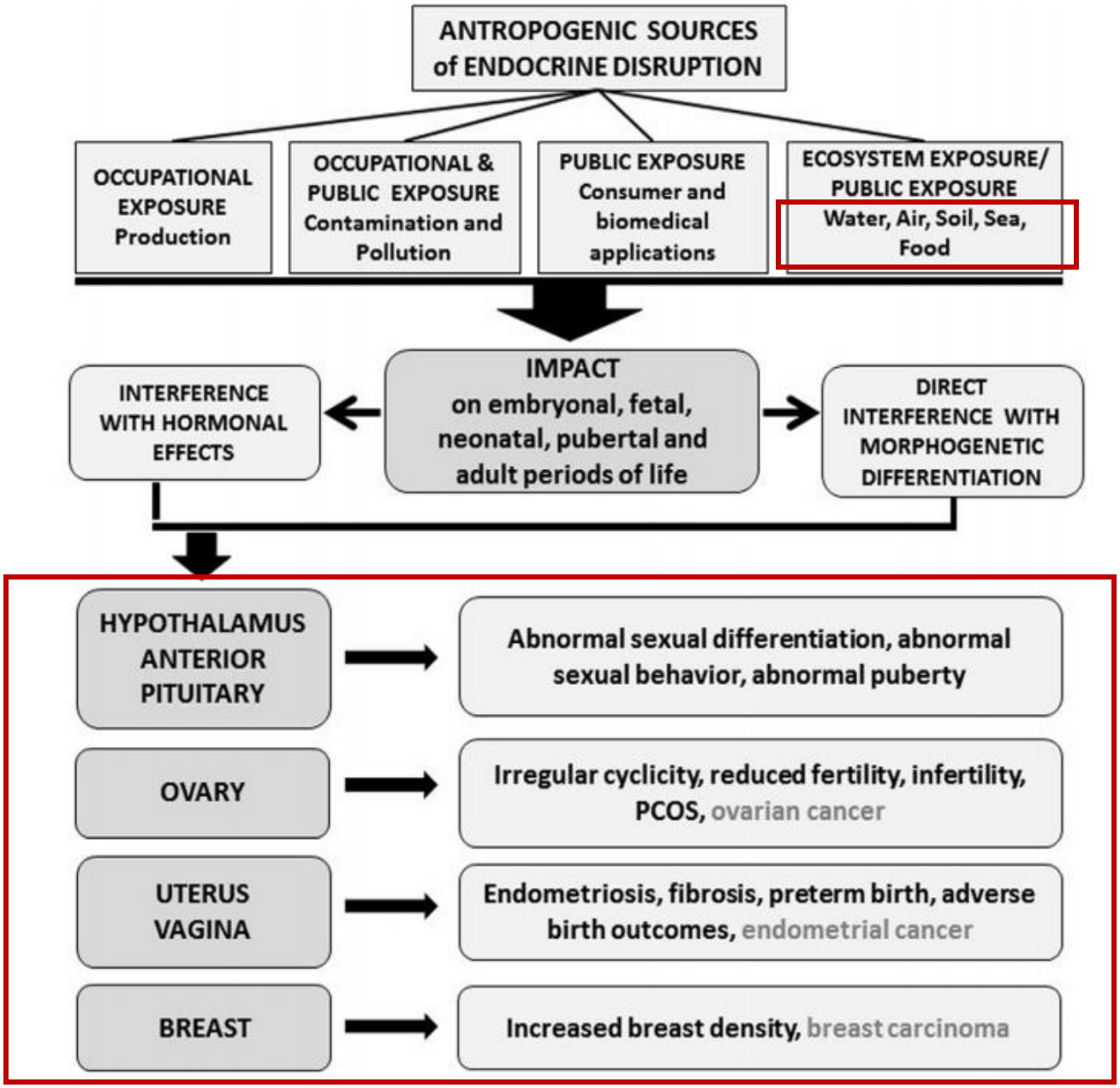
increasing the level of oxidative stress

DBP: inhibits the expression of cyclin E1, cyclin A2 and cyclin B1

-> **cell cycle arrest and inhibition** of antral follicle growth

BPA: **apoptosis via a caspase-3-**mediated mechanism in female rat

Human exposure to endocrine disrupting chemicals (EDCs) and possible toxic influences on female neuroendocrine reproductive system



➢ Very little is known about the reproductive health risks associated with EDC mixtures.

- **Variable persistence** of EDCs in the body and the environment,
- **The timing of exposure**

-great importance since the same dosage exerts diverse effects in individuals of different age.

-**Windows of susceptibility**: in utero, adolescence, adulthood

- **non-monotonic dose-response relationship**
- The results may appear **immediately, and/or they may manifest later in life and in the following generations**, with different susceptibility, depending on the genetic polymorphisms of the exposed individuals.

Hypothalamic-pituitary-gonadal axis

- Animal studies suggest that EDCs may disrupt the orderly programmed progression of female reproductive life cycle through developmental changes of **kisspeptin-GPR54 system**
- Reduction of hypothalamic kisspeptin-immunoreactivity in hypothalamic nu-clei in adult rats perinatally exposed to estradiol benzoate (EB; 50 mg/kg), genistein (10 mg/kg b.w.), BPA (500 mg/kg b.w.) or PCB mixture (1 mg/kg) has been shown to **advance the puberty onset and accelerate reproductive senescence**
- Developmental exposure to some EDCs can advance the time of vaginal opening independently of kisspeptin signaling

Puberty

- **<u>Precocious puberty (early menarche)</u>**: associated with exposure to EDCs in girls from the U.S.A., Belgium, Puerto Rico or Taiwan, although the evidence is contradictory.
- **spectrum of puberty disorders**

- early onset puberty, and precocious or delayed puberty, along with concomitant disorders of sexual differentiation

- **Most of the evidence from animal experiments and *in vitro* studies**

-actions at different levels, including the neuroendocrine signals, hypothalamic-pituitary axis, gonads and peripheral target organs such as breasts, uterus, genitals and hair follicles

Ovarian disorders

Significant in vivo association between **higher EDCs** (PCBs, polybrominated diphenyl ethers, organochlorine pesticides) **concentrations in the follicular fluid of women** and **reduced developmental competence of their oocytes, a highly significant drop in fertilization rate and lower proportion of top-quality embryos**, independent of the age, BMI, E2 levels of the patient, fertilization procedure or the presence of male subfertility has been demonstrated *(Petro EM,2012).*

Ovarian disorders

- **BPA appears to stimulate ovarian theca-interstitial cells to produce androgens**, possibly by regulating 17b-hydroxylase, a key enzyme in gonadal steroid biosynthesis which dysregulation results in the overproduction of androgens by the ovary *(Barrett ES, 2014)*

- There is *evidence in animal models* that many **EDCs lead to multioocyte follicles (BPA, DES) being a potential precursor of premature ovarian follicles** *(Costa EM, 2014)*

Endometriosis

- In several case-control studies, **significantly higher plasma levels** of mono-(2-ethylhexyl) phthalate (MEHP) and di(2-ethylhexyl) phthalate (DEHP), mono-n-butyl phthalate (MBP), dioxin-like PCBs, or pesticides (mirex, hexachlorocyclohexane, HCH) and fungicides (t-nonachlor, hexachlorobenzene)
- **DEHP has suggested increased viability of endometrial stromal cells**, a precondition to endometriosis.
- TCDD disrupted cannabinoid signaling leading to inflammation in endometrium.
- **Promoted invasiveness of stromal endometrial cells** by increased expression of matrix metalloproteinase-2 and -9 (MMP-2, MMP-9) and reduced expression of CD82 (tumor metastasis suppressor) that inhibits the invasiveness of endometrial cells has been observed *(Gore AC, 2015)*

Fibroids

- Positive association between higher concentrations of BPA, nonylphenol (NP), and octylphenol(OP) and fibroids has been shown in a recent study in Chinese women
- A recent cross-sectional investigation of phthalates exposures reported a positive association between MBP and an increased risk of fibroids, but an inverse association between MEHP derivatives and tumors.
- **MEHP exposure and GSTM1 null genotype** are associated with fibroids.

Environmental exposure to polycyclic aromatic hydrocarbons (PAHs): The correlation with and impact on reproductive hormones in umbilical cord serum☆

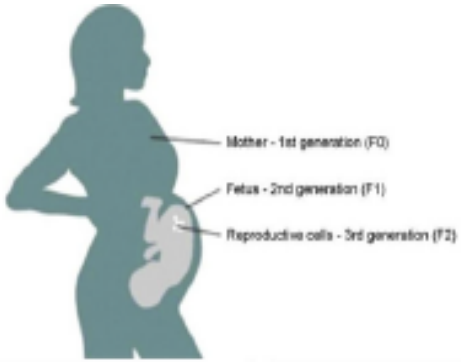
Shanshan Yin, Mengling Tang, Fangfang Chen, Tianle Li, Weiping Liu*

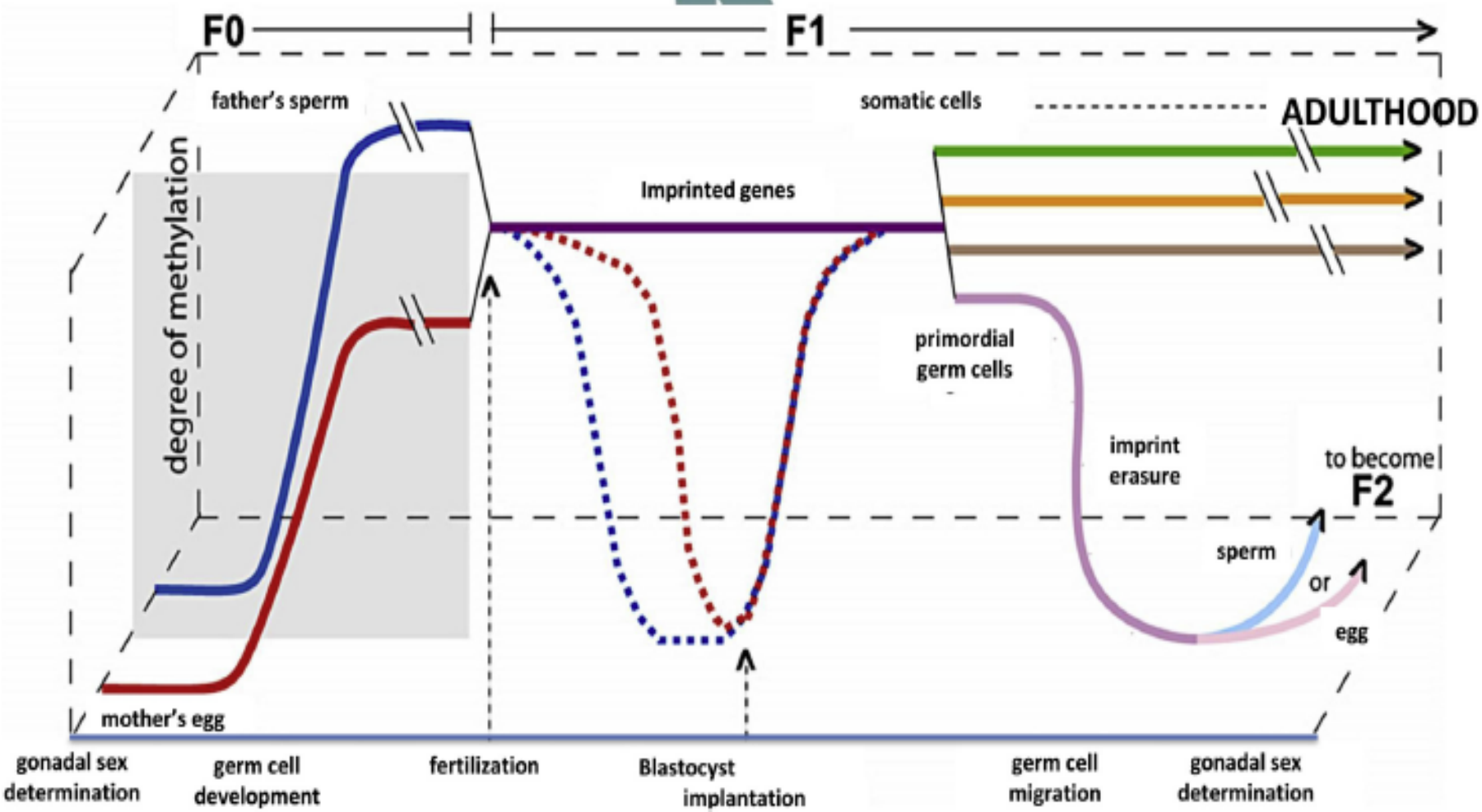
Reproductive hormone concentrations in the research population (n = 77).

Reproductive hormones	N	Mean ± SD	Percentiles		
			25	50	75
FSH (mIU mL^{-1})	77	12.2 ± 9.80	3.68	9.57	19.9
LH (mIU mL^{-1})	77	21.4 ± 19.0	5.25	18.3	30.1
Testo (ng ml^{-1})	77	7.17 ± 9.54	0.861	5.25	10.83
AMH (pg ml^{-1})	77	1056 ± 719	486	1023	1408
E2 (ng ml^{-1})	77	2.60 ± 2.19	1.06	2.13	3.72

The exposure to **PAHs negatively affected estradiol (E2) and Anti-Mullerian hormones (AMH) and positively affected FSH in the umbilical cord serum.** These results may help to understand the complex pathways involved in disorders of human reproductive health associated with prenatal exposure to PAHs.

Environmental toxicants: hidden players on the reproductive stage





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Grand-maternal smoking in pregnancy and grandchild's autistic traits and diagnosed autism.

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Abstract

Although there is considerable research into the genetic background of autism spectrum disorders, environmental factors are likely to contribute to the variation in prevalence over time. Rodent experiments indicate that environmental exposures can have effects on subsequent generations, and human studies indicate that parental prenatal exposures may play a part in developmental variation. Here we use the Avon Longitudinal Study of Parents and Children (ALSPAC) to test the hypothesis that if the mother or father (F1) had been exposed to their own mother's (F0) smoking during pregnancy, the offspring (F2) would be at increased risk of autism. We find an association between maternal grandmother smoking in pregnancy and grand daughters having adverse scores in Social Communication and Repetitive Behaviour measures that are independently predictive of diagnosed autism. In line with this, we show an association with actual diagnosis of autism in her grandchildren. Paternal grandmothers smoking in pregnancy showed no associations.

- Data demonstrate that EDCs may contribute to numerous human female reproductive disorders.
- **Time of exposure is as important** as exposed dose, duration of exposure, and age for EDCs able to disrupt endocrine functions.
- Animal and human studies regarding reproductive disorders are **still insufficient**
- **More systematic research in this area** is critical to our understanding of human health risks.
- **Effective protection** from chemical exposures requires leadership, environmental, education, civic participation, and social action.

Conclusions